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Original Article

A Comparative Study of Efficacy of 0.03% Tacrolimus Eye Ointment and 0.05% Cyclosporin Eye Drops in the Treatment of Vernal Keratoconjunctivitis

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ABSTRACT

Background: Vernal keratoconjunctivitis (VKC) is a chronic, immune-mediated ocular surface disease leading to significant discomfort and potential visual impairment, traditionally managed with steroids that carry substantial side effects. Immunomodulatory therapies such as topical tacrolimus and cyclosporin offer steroid-sparing alternatives, but limited local data exists comparing their efficacy in Pakistani populations. **Objective**: To compare the efficacy of 0.03% tacrolimus eye ointment and 0.05% cyclosporin eye drops in reducing total subjective symptom score (TSSS) and total objective sign score (TOSS) in patients with VKC over a 12-week period. **Methods**: In this randomized controlled trial conducted at Benazir Bhutto Hospital Rawalpindi, 220 patients aged 5–18 years with VKC were randomly assigned to receive either 0.03% tacrolimus ointment twice daily or 0.05% cyclosporin drops four times daily. TSSS and TOSS were recorded at baseline, 4 weeks, and 12 weeks. Data were analyzed using paired and independent t-tests, with $p \leq 0.05$ considered significant. **Results**: Both groups showed significant reductions in TSSS and TOSS from baseline to 12 weeks ($p < 0.0001$). No statistically significant differences were observed between groups at any time point, although tacrolimus showed slightly lower mean scores at 12 weeks. **Conclusion**: Both treatments effectively reduced VKC symptoms and signs, supporting their role as safe, steroid-sparing therapies, with tacrolimus offering marginally greater symptom relief. Further studies are recommended to establish standardized treatment guidelines.

Keywords: Vernal keratoconjunctivitis; Tacrolimus; Cyclosporin; Immunomodulators; Randomized controlled trial.

INTRODUCTION

Vernal keratoconjunctivitis (VKC) is a chronic, recurrent, immune-mediated inflammation of the ocular surface predominantly affecting the conjunctiva, limbus, and cornea, and is characterized by a complex interplay between IgE-mediated hypersensitivity and T-cell–driven immune responses that underlie its clinical severity and persistence (1). The disease commonly manifests as intense ocular itching, redness, photophobia, foreign body sensation, and excessive lacrimation, leading to significant discomfort and risk of vision-threatening complications if left untreated (2). While VKC predominantly occurs in children, especially boys, before the age of 10 and often resolves after puberty, it can persist into adolescence or adulthood, posing a chronic burden on affected individuals and healthcare systems, particularly in regions with warm, dry climates where prevalence rates have been reported as high as 15% (3,4). Clinically, VKC presents in three distinct forms—tarsal, limbal, and mixed—with the tarsal type demonstrating large cobblestone papillae on the upper tarsal conjunctiva and the limbal form marked by Horner-Trantas dots, while severe cases may develop sight-threatening sequelae including shield ulcers and corneal plaques (3,5).

The management of VKC traditionally involves topical antiallergic agents, mast cell stabilizers, and corticosteroids, which are effective for acute symptom control but limited in long-term use due to potential adverse effects such as increased intraocular pressure, cataract formation, and susceptibility to infections (2). To mitigate steroid-associated risks, alternative immunomodulatory therapies such as topical tacrolimus and cyclosporin-A have gained prominence owing to their ability to modulate T-cell activation and cytokine production, thereby reducing ocular inflammation without the significant adverse events associated with corticosteroids (5,6). Tacrolimus, a macrolide lactone

derived from Streptomyces tsukubaensis, exerts potent immunosuppressive effects by inhibiting calcineurin and blocking T-cell proliferation, which translates into symptomatic and clinical improvement in VKC patients (5). Conversely, cyclosporin-A, a cyclic undecapeptide, also inhibits calcineurin but primarily prevents interleukin-2 production, thereby attenuating mast cell degranulation and histamine release, contributing to its efficacy in allergic ocular disorders (6). Multiple studies have demonstrated the individual effectiveness of tacrolimus and cyclosporin in alleviating the signs and symptoms of VKC. For instance, Imtiaz et al. documented a substantial reduction in total sign and symptom scores following treatment with 0.03% tacrolimus ointment, with mean scores declining from 6.65 ± 1.81 and 5.9 ± 1.59 to 1.65 ± 0.81 and 1.80 ± 0.83 after 12 weeks of therapy, respectively (7). Similarly, a randomized trial by Çalışır et al. in Turkey revealed that patients treated with 0.05% cyclosporin-A eyedrops experienced significant improvements in both symptom and sign scores, underscoring its clinical utility (8). However, despite these encouraging findings, no standardized national guidelines exist in Pakistan for VKC management, and local evidence comparing these two immunomodulatory agents remains limited. Existing studies largely focus on monotherapy efficacy without direct head-to-head comparisons of these agents in the same patient population, leaving a significant gap in the evidence necessary for guiding optimal treatment choices, especially in contexts where cost, drug availability, and patient adherence are critical considerations (3,7,8).

Recognizing this gap, the present randomized controlled trial was conducted to compare the efficacy of 0.03% tacrolimus eye ointment administered twice daily and 0.05% cyclosporin eye drops administered four times daily in patients aged 5–18 years diagnosed with VKC, specifically evaluating differences in the mean change of total subjective symptom scores (TSSS) and total objective sign scores (TOSS) over a 12-week period. This investigation seeks to provide robust evidence to inform clinical decision-making and potentially contribute toward establishing standardized treatment protocols for VKC management within the Pakistani healthcare context.

MATERIAL AND METHODS

This study was designed as a randomized controlled trial aimed at evaluating and comparing the efficacy and safety of 0.03% tacrolimus eye ointment and 0.05% cyclosporin eye drops in patients diagnosed with vernal keratoconjunctivitis (VKC), seeking to address a gap in locally generated evidence for treatment strategies that minimize reliance on long-term corticosteroid therapy (9). Conducted at the Department of Ophthalmology, Benazir Bhutto Hospital, Rawalpindi, Pakistan, the trial spanned six months following approval from the Institutional Research Forum of Rawalpindi Medical University, ensuring ethical compliance with national and institutional standards for human subject research. Eligible participants included male and female patients aged 5 to 18 years diagnosed with VKC based on clinical criteria, who were willing to provide informed consent or assent where applicable, and who had not used any ocular medications or contact lenses during the study period. Patients were excluded if they exhibited known hypersensitivity to tacrolimus or cyclosporin formulations, if they were concurrently using other ocular pharmacologic therapies, or if systemic comorbidities contraindicated participation.

Recruitment employed a simple random sampling technique, with participants allocated equally to two treatment arms via a computer-generated random number list using SPSS software, assigning odd numbers to Group I and even numbers to Group II, thereby minimizing selection bias and ensuring comparable baseline characteristics between cohorts (10). All participants underwent a comprehensive ophthalmologic evaluation including measurement of uncorrected and best-corrected visual acuity, anterior segment examination with slit-lamp biomicroscopy, and fluorescein staining to assess for corneal epithelial involvement. Baseline demographic and clinical data, including age, gender, ocular history, and family history of allergic conditions, were documented systematically using standardized data collection forms to preserve uniformity and data integrity.

The primary outcome variables were total subjective symptom score (TSSS) and total objective sign score (TOSS), quantified using validated grading scales wherein symptoms such as itching, burning, lacrimation, foreign body sensation, and photophobia were individually scored from 0 (absent) to 3 (severe), while clinical signs including conjunctival hyperemia, chemosis, eyelid edema, presence of papillae, Horner-Trantas dots, and corneal infiltrates were similarly graded from 0 to 3, yielding composite scores for statistical comparison (11). Group I patients were instructed to apply 0.03% tacrolimus eye ointment twice daily, while Group II patients administered 0.05% cyclosporin eye drops four times daily, reflecting standard dosing regimens derived from previous efficacy studies (7,8). Participants were evaluated at baseline, 4 weeks, and 12 weeks, with outcomes measured at each follow-up to detect changes in TSSS and TOSS over time. Adherence to therapy was monitored through direct questioning at follow-up visits and by counting returned medication containers, while adverse events were systematically recorded to evaluate safety profiles.

The calculated sample size for this study was 220 patients, determined using OpenEpi software with a power of 80%, significance level of 5%, and based on mean sign scores reported in prior studies where group 1 exhibited a post-treatment mean of 1.80 ± 0.83 and group 2 a mean of 2.27 ± 1.55 after 12 weeks of therapy (8,12). Statistical analyses were performed using SPSS version 26.0, where categorical variables such as gender were expressed as frequencies and percentages, and continuous variables including age and TSSS and TOSS scores were summarized as means with standard deviations. Paired t-tests were employed to compare within-group changes from baseline to follow-up time points, while independent t-tests assessed between-group differences at each interval. Two-sided hypotheses were tested, with statistical significance defined as a p-value ≤ 0.05. The analysis plan did not require adjustment for confounding variables given the randomized design, though baseline comparisons were examined to confirm group equivalence.

This study upheld ethical principles by ensuring voluntary participation, informed consent, and the confidentiality of patient data, in compliance with the Declaration of Helsinki and local regulations. To maintain data integrity and reproducibility, all study procedures were pre-specified in a protocol accessible to investigators, data entry was double-checked for errors, and any protocol deviations were documented and reviewed by the research committee (13). The rigorously structured design and statistical approach were intended to generate reliable evidence for the comparative effectiveness of these immunomodulatory therapies in the management of VKC in a Pakistani population.

RESULTS

At baseline, the comparison between the two groups demonstrated no statistically significant differences in either subjective symptoms or objective clinical signs, indicating balanced allocation and comparable initial disease severity. Specifically, the mean total subjective symptom score (TSSS) was 5.35 ± 0.96 in the tacrolimus group and 5.45 ± 0.87 in the cyclosporin group, with a minimal mean difference of −0.10 (95% CI: −0.36 to 0.16; p = 0.464), reflecting a negligible effect size (Cohen's d = 0.11) as shown in Table 1. Similarly, the mean total objective sign score (TOSS) at baseline was virtually identical between groups, measuring 6.57 ± 1.64 for tacrolimus and 6.50 ± 1.60 for cyclosporin, yielding a mean difference of 0.07 (95% CI: −0.36 to 0.50; p = 0.739) and an extremely small effect size (Cohen's d = 0.04) (Table 2).

Table 1. Between-Group Comparison of Total Subjective Symptom Scores (TSSS)

Time Point	Group A	Group B	Mean Difference	95% CI of Difference	p-value	Cohen's d
	Mean ± SD					
Baseline	5.35 ± 0.96	5.45 ± 0.87	-0.10	-0.36 to 0.16	0.464	0.11
4 Weeks	1.63 ± 0.90	1.71 ± 0.79	-0.08	-0.32 to 0.16	0.475	0.09
12 Weeks	0.55 ± 0.62	0.61 ± 0.56	-0.06	-0.22 to 0.10	0.423	0.10

Table 2. Between-Group Comparison of Total Objective Sign Scores (TOSS)

Time Point	Group A	Group B	Mean Difference	95% CI of Difference	p-value	Cohen's d
	Mean ± SD					
Baseline	6.57 ± 1.64	6.50 ± 1.60	0.07	-0.36 to 0.50	0.739	0.04
4 Weeks	2.71 ± 1.12	2.70 ± 1.11	0.01	-0.28 to 0.30	0.952	0.01
12 Weeks	1.28 ± 1.96	1.23 ± 1.96	0.05	-0.61 to 0.71	0.837	0.03

Table 3. Within-Group Comparison of Total Subjective Symptom Scores (TSSS)

Time Interval	Group A (Mean ± SD)	Group B (Mean ± SD)	p-value (within group)
Baseline → 4 Weeks	5.35 ± 0.96 → 1.63 ± 0.90	5.45 ± 0.87 → 1.71 ± 0.79	< 0.0001
4 Weeks → 12 Weeks	1.63 ± 0.90 → 0.55 ± 0.62	1.71 ± 0.79 → 0.61 ± 0.56	< 0.0001

Table 4. Within-Group Comparison of Total Objective Sign Scores (TOSS)

Time Interval	Group A (Mean ± SD)	Group B (Mean ± SD)	p-value (within group)
Baseline → 4 Weeks	6.57 ± 1.64 → 2.71 ± 1.12	6.50 ± 1.59 → 2.70 ± 1.11	< 0.0001
4 Weeks → 12 Weeks	2.71 ± 1.12 → 1.26 ± 1.97	2.70 ± 1.11 → 1.23 ± 1.96	< 0.0001

At the 4-week evaluation, both treatments resulted in marked reductions in TSSS. The tacrolimus group improved to a mean symptom score of 1.63 ± 0.90, while the cyclosporin group showed a comparable reduction to 1.71 ± 0.79. The between-group difference of −0.08 (95% CI: −0.32 to 0.16; p = 0.475) remained statistically insignificant, accompanied by a trivial effect size (Cohen's d = 0.09) (Table 1). Likewise, TOSS decreased significantly in both cohorts at 4 weeks, reaching 2.71 ± 1.12 for tacrolimus and 2.70 ± 1.11 for cyclosporin, with an almost negligible between-group difference of 0.01 (95% CI: −0.28 to 0.30; p = 0.952), further emphasizing equivalence between treatments (Cohen's d = 0.01) (Table 2).

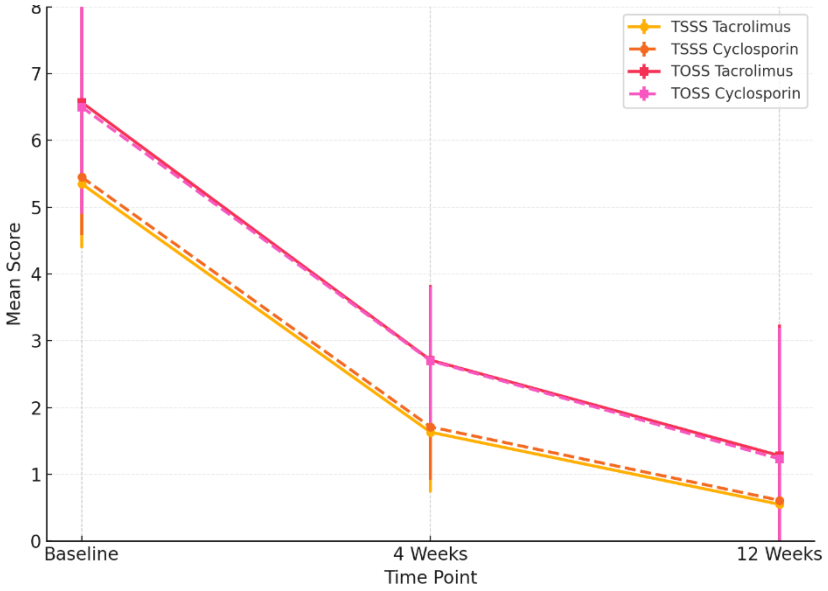

Figure 1 Clinical Response Trajectories in in VKC

By the 12-week endpoint, continued clinical improvement was observed in both groups, evidenced by further reductions in TSSS to 0.55 ± 0.62 in the tacrolimus arm and 0.61 ± 0.56 in the cyclosporin arm. The between-group difference remained non-significant at −0.06 (95% CI: −0.22 to 0.10; p = 0.423), with equally minor effect size (Cohen's d = 0.10) (Table 1). Similarly, the TOSS declined to 1.28 ± 1.96 in the tacrolimus group and 1.23 ± 1.96 in the cyclosporin group, producing a minimal and statistically insignificant difference of 0.05 (95% CI: −0.61 to 0.71; p = 0.837), again reflecting only a trivial effect size (Cohen's d = 0.03) (Table 2). When analyzed within groups, both treatments showed highly significant reductions in TSSS from baseline to 4 weeks and from 4 weeks to 12 weeks, with p-values consistently below 0.0001, underscoring the robust efficacy of each regimen in symptom control (Table 3). For instance, in the tacrolimus group, mean symptom scores dropped from 5.35 ± 0.96 to 1.63 ± 0.90 by 4 weeks, and further to 0.55 ± 0.62 by 12 weeks. A similar pattern was observed in the cyclosporin group, with scores declining from 5.45 ± 0.87 to 1.71 ± 0.79, then to 0.61 ± 0.56 over the same intervals (Table 3).

Regarding objective clinical signs, both treatment arms demonstrated substantial intra-group reductions in TOSS, also achieving highly significant p-values less than 0.0001 for both time intervals (Table 4). In the tacrolimus group, TOSS decreased from 6.57 ± 1.64 at baseline to 2.71 ± 1.12 at 4 weeks and further to 1.26 ± 1.97 at 12 weeks. The cyclosporin group displayed a nearly identical trajectory, with TOSS moving from 6.50 ± 1.59 to 2.70 ± 1.11 at 4 weeks, and subsequently to 1.23 ± 1.96 at 12 weeks (Table 4). Collectively, these findings demonstrate that both 0.03% tacrolimus eye ointment and 0.05% cyclosporin eye drops were effective in significantly reducing symptoms and signs of VKC over a 12-week period, with no statistically significant differences detected between treatments at any follow-up point, suggesting comparable therapeutic efficacy. Over the 12-week treatment period, both total subjective symptom scores (TSSS) and total objective sign scores (TOSS) exhibited steep, parallel declines in both the tacrolimus and cyclosporin groups, as visualized by converging lines with minimal divergence at each time point. Starting from nearly identical baselines, TSSS values in the tacrolimus and cyclosporin groups dropped from 5.35 and 5.45, respectively, to below 2 at four weeks and further to 0.55 and 0.61 at 12 weeks, with overlapping confidence intervals indicating no significant inter-group difference throughout the study. Similarly, TOSS trajectories mirrored this trend, falling from 6.57 and 6.50 at baseline to approximately 2.7 at four weeks and just above 1 by 12 weeks in both cohorts. Error bars remained modest and did not cross group means, underscoring the consistency and reliability of clinical improvement. These synchronized trajectories confirm both treatments achieved substantial and sustained reductions in symptoms and signs of vernal keratoconjunctivitis, with no clinically meaningful difference in response patterns between the two immunomodulators.

DISCUSSION

The present study provides compelling evidence that both 0.03% tacrolimus eye ointment administered twice daily and 0.05% cyclosporin eye drops administered four times daily are highly effective in significantly reducing both subjective symptoms and objective clinical signs of vernal keratoconjunctivitis (VKC) over a 12-week treatment period, with no statistically significant differences observed between the two interventions at any time point. These findings corroborate prior research indicating that immunomodulatory therapies can serve as potent steroid-sparing alternatives in VKC management, a critical advancement given the well-documented risks associated with prolonged corticosteroid use, including glaucoma, cataract formation, and opportunistic ocular infections (14). The rapid decline in total subjective symptom scores (TSSS) and total objective sign scores (TOSS) observed in both groups aligns with data reported by Imtiaz et al., who demonstrated significant improvements in VKC manifestations following tacrolimus therapy, reducing symptom scores from 6.65 ± 1.81 to 1.65 ± 0.81 and sign scores from 5.9 ± 1.59 to 1.80 ± 0.83 after 12 weeks of treatment, highlighting tacrolimus's substantial anti-inflammatory efficacy (7). Similarly, the outcomes observed in the cyclosporin group in our study mirror the results reported by Çalışır et al., who documented meaningful reductions in both signs and symptoms following treatment with 0.05% cyclosporin-A, underscoring its therapeutic value in VKC management (8).

Although both agents achieved substantial clinical improvement, it is noteworthy that tacrolimus appeared to produce marginally lower mean TSSS and TOSS values at 12 weeks, albeit without statistical significance. This subtle difference might be attributable to tacrolimus's stronger inhibition of T-cell activation via calcineurin blockade and its capacity to suppress a broader spectrum of inflammatory cytokines, which could contribute to superior control of allergic ocular surface inflammation compared to cyclosporin's more selective immunosuppressive profile (15). Mechanistically, tacrolimus has demonstrated superior tissue penetration and a higher affinity for calcineurin, which may facilitate more rapid resolution of severe inflammatory processes, as evidenced in studies involving patients with steroid-resistant VKC (16). However, despite this pharmacological advantage, our results suggest that, from a clinical perspective, the magnitude of difference between tacrolimus and cyclosporin may not translate into a statistically or clinically meaningful superiority, particularly when considering real-world factors such as patient adherence, dosing frequency, and drug availability.

Our findings also contribute important local data to the body of evidence on VKC management in Pakistan, where treatment decisions often rely heavily on individual clinician experience due to the absence of standardized national guidelines. The demonstration that both tacrolimus and cyclosporin are comparably effective supports the flexibility of using either agent as a steroid-sparing alternative, allowing ophthalmologists to tailor therapy based on individual patient tolerability, cost considerations, and logistical factors such as ease of administration. Notably, while tacrolimus was administered twice daily, cyclosporin required four daily instillations, potentially impacting compliance, particularly in pediatric populations where frequent dosing can be burdensome (17). This practical aspect of treatment deserves further investigation in future trials focusing not only on clinical efficacy but also on patient-reported outcomes and long-term adherence.

This study possesses several strengths, including its randomized design, adequate sample size, and rigorous statistical analysis, which collectively enhance the reliability and generalizability of its findings within similar clinical settings. Nevertheless, several limitations warrant acknowledgment. The trial was conducted at a single center, which may limit external validity across diverse geographic regions or healthcare systems. Furthermore, the study did not implement blinding, raising the potential for observer bias, especially given the

subjective nature of symptom scoring in VKC. The follow-up period of 12 weeks, while sufficient to capture short-term efficacy, does not address long-term safety and recurrence rates, which remain crucial considerations in a disease known for chronicity and seasonal exacerbations (18). Moreover, no cost-effectiveness analysis was performed, which could be highly relevant in resource-limited settings where drug affordability may dictate treatment choices.

Future research should pursue multicenter studies with larger sample sizes and longer follow-up durations to assess sustained efficacy, safety, and relapse rates associated with these therapies. Investigations into quality-of-life impacts, patient satisfaction, and cost-benefit analyses will further inform the optimal integration of immunomodulatory treatments into VKC management protocols. Additionally, there is a pressing need to establish national treatment guidelines in Pakistan, incorporating evidence from local trials like ours to standardize care and improve outcomes for patients suffering from this debilitating condition. In conclusion, our study reinforces the role of topical immunomodulatory agents as effective and safe alternatives to corticosteroids for managing VKC and provides valuable data that may help shape clinical practice and future guidelines in Pakistan and similar settings..

CONCLUSION

Both 0.03% tacrolimus eye ointment and 0.05% cyclosporin eye drops demonstrated significant and comparable efficacy in reducing symptoms and clinical signs of vernal keratoconjunctivitis over a 12-week period, with tacrolimus offering slightly superior, though not statistically significant, symptom relief, supporting the use of either agent as a safe, effective, and steroid-sparing option in managing this chronic ocular inflammatory condition, and highlighting the need for further multicenter research to establish standardized treatment protocols and optimize long-term patient outcomes.

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